HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2024 April 18.

Published in final edited form as:

Environ Int. 2019 October ; 131: 105067. doi:10.1016/j.envint.2019.105067.

Temperature, placental abruption and stillbirth

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Abstract

Background: Pregnant women may be vulnerable to changes in ambient temperature and warming climates. Recent evidence suggests that temperature increases are associated with placental abruption, a risk factor for stillbirth.

Objectives: We investigated the effect of acute exposures to apparent temperature on stillbirths in Harris County, Texas, 2008–2013.

Methods: We conducted a case-crossover study to investigate the association between temperature and stillbirth among 708 women. We used data from the National Climatic Data Center to estimate maternal exposure to daily average apparent temperature over the days (lag days 1 through 6) preceding the stillbirth event. We employed symmetric bidirectional sampling to select six control periods one to three weeks before and after each event and applied conditional logistic regression to examine associations between increases of apparent temperature and stillbirths during the warm season (May–September). We adjusted for fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3) and used stratified analysis

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Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105067.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

to examine differences in risk by maternal race/ethnicity. We also examined the association among stillbirths with and without placental abruptions.

Results: Independent of air pollutant exposures, a 10 °F increase in apparent temperature in the week preceding delivery (lag days 1 to 6) was positively associated with a 45% (adjusted OR = 1.45, 95% confidence interval (CI): 1.18, 1.77) increase in risk for stillbirth. Risks were elevated for stillbirths occurring in June through August, for Hispanic and non-Hispanic Black women, but not for non-Hispanic Whites. We also observed elevated risks associated with temperature increases in the few days preceding delivery among stillbirths caused by placental abruption, with the risk being highest on lag day 1 (OR = 1.93, 95% CI: 1.15, 3.23).

Conclusions: Independent of maternal ambient air pollutant exposure, we found evidence of an association between apparent temperature increases in the week preceding an event and risk of stillbirth. Risks for stillbirth varied by race/ethnicity. Further, in the first study to evaluate the impact of temperature on a specific complication during pregnancy, the risks were higher among mothers with placental abruption.

Keywords

Temperature; Stillbirth; Placental abruption

1. Introduction

Pregnant women are particularly vulnerable to environmental stressors associated with climate change, such as heat exposures (Rylander et al., 2013; Poursafa et al., 2015; Kuehn and McCormick, 2017). The number of studies that have examined the association between ambient temperature and stillbirth (Strand et al., 2012; Arroyo et al., 2016; Basu et al., 2016; Auger et al., 2017; Ha et al., 2017; Li et al., 2018) is growing, with two conducted within the United States (U.S.) (Basu et al., 2016; Ha et al., 2017) and four in Spain, Canada and Australia (Strand et al., 2012; Arroyo et al., 2016; Auger et al., 2017; Li et al., 2018). Two investigations have examined temperature fluctuations over long gestational periods (i.e., months or trimesters) and observed an increase in risk for stillbirth associated with elevated temperatures (Strand et al., 2012; Li et al., 2018). To evaluate the acute effect of elevated ambient temperature on stillbirth, two case-crossover studies in the U.S. reported that increases in temperature in the week preceding delivery during the warm season were associated with increases in stillbirth risk (Basu et al., 2016; Ha et al., 2017). Further, a case-crossover study in Quebec, Canada examined maximum daily temperature increases in the day preceding an intrauterine fetal death and reported similar findings, also during the warm season (Auger et al., 2017).

Reported causes of stillbirth are varied and may include placental, fetal or umbilical cord abnormalities, maternal medical conditions and obstetric complications (Stillbirth Collaborative Research Network Writing Group, 2011). Pathologic studies have examined causal or contributory links between placental abruptions and stillbirth (Ptacek et al., 2014) and a recent systematic review found that abruption was the most frequently reported risk factor for stillbirth, among other neonatal and perinatal outcomes (Downes et al., 2017). Placental abruption may occur if the integrity of the placenta is compromised by, for example, heat and dehydration, since pregnant women's ability to regulate their body temperature may be compromised given their unique physiological characteristics (Strand et al., 2011a). Interestingly, in the single study investigating the association between elevated ambient temperatures and placental abruption to date, He et al. (2018) reported a 7% (0.99%, 1.16%) increase in risk of abruption associated with a weekly maximum temperature of 30 degrees Celsius (°C) compared to 15 °C (or 86 °F compared to 59 °F) during the week before an abruption event, and the risk was independent of exposures to ambient air pollutants. Further, heat stress may also lead to placental inflammation (Schifano et al., 2013), which is associated with placental abruption and could lead to preterm labor and premature rupture of membranes, which some fetuses might not be able to tolerate (Pinar et al., 2014).

Given the limited evidence regarding the ambient temperature-stillbirth association, we designed a case-crossover study using symmetric bidirectional sampling to examine associations between temperature and stillbirths among women in Harris County, Texas, an area characterized by higher temperatures and humidity compared to previous studies. The underlying hypothesis was that women who experience higher temperatures in the few days before delivery were more likely to have a stillborn delivery than women who did not experience such temperatures. Given the putative link between temperature, placental abruption and stillbirth, a secondary objective was to examine this association among stillbirths with and without placental abruption.

2. Methods

2.1. Study population

This study was approved by The University of Texas Health Science Center at Houston (UTHealth) Committee for the Protection of Human Subjects and the Texas Department of State Health Services (DSHS) Institutional Review Board. Using fetal death records from the Texas DSHS, we abstracted the following information for 1874 singleton stillborn deliveries occurring between January 1, 2008 and December 31, 2013 for all mothers residing in Harris County, Texas: maternal age (< 20, 20–24, 25–29, 30–34, 35–30 and ≥ 40 years), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other/unknown), and maternal education (high school or less, some college, college or beyond). We also abstracted information on smoking (no smoking before or during pregnancy, smoking three months before and during pregnancy), pre-pregnancy body mass index (BMI)(weight (kg)/height (m^2)); classified as < 18.5, 18.5 to 24.9, 25.0 to 29.9, 30.0 to 34.9, and ≥ 35), residential address and placental abruption. Following exclusions: for missing gestational age or birth weight (n = 10; < 1%); for gestational age < 20 or > 44 weeks (n = 123; < 1%); and to avoid fixed cohort bias, where we excluded pregnancies with conception dates > 20 weeks or < 44 weeks before the study start and end dates (n = 142; < 1%) (Strand et al., 2011b), a total of 1599 stillbirths remained for analysis, of which 709 (44.3%) were delivered in the warm season (May through September). We classified the cause of stillbirths as placental abruption if the fetal death certificate indicated placental abruption as either the initiating or contributing cause of death. Of the 709 cases of stillbirth, 87 (12.27%) were caused by placental abruption.

2.2. Study design

We used a case-crossover design, where each case serves as her own matched control, and therefore did not adjust for sociodemographic characteristics or maternal risk factors that are relatively constant, such as race/ethnicity or smoking status (Maclure, 1991; Maclure and Mittleman, 2000). The average period for delivery following an intrauterine death has been estimated at 48 h (Gardosi et al., 1998) and the median time at < 24 h (Genest et al., 1992). We therefore defined each case period starting on lag day 1 (one day preceding the stillborn delivery) through lag day 6. We applied a symmetric bidirectional sampling approach (Bateson and Schwartz, 1999; Maclure and Mittleman, 2000) to assign six control periods per each case period, selecting three control periods on the first, second and third preceding weeks and three control periods over the first, second and third subsequent weeks of the stillbirth event. We also defined control periods as lag days 1 through 6.

2.3. Apparent temperature and air pollution data

We obtained meteorological data for January 1, 2007 to December 31, 2013 from the National Climatic Data Center (2017) for seven weather stations from the Houston-Galveston-Brazoria region, which is spread over eight contiguous counties, including Harris County, where the study population comes from. We calculated mean daily apparent temperature (in degrees Fahrenheit; °F) using hourly ambient and dew point temperature based on methods previously described by Basu et al. (2008). There were little differences in the mean daily temperatures and standard deviations across the seven meteorological stations so apparent temperature for each day of the pregnancy was computed using a single meteorological station in Harris County.

Because there is also suggestive evidence of an association between maternal exposure to ambient air pollutants and stillbirth (Glinianaia et al., 2004; Lacasana et al., 2005; Siddika et al., 2016), we also obtained hourly concentration measurements from all active Texas Commission on Environmental Quality (TCEQ) monitoring stations in the study area. We excluded two $PM_{2.5}$ monitors, one O_3 monitor and one NO_2 monitor that had > 25% missing observations over the study period, which left 13 monitors for $PM_{2.5}$ (reported in μg/m^3), 48 monitors for O_3 (ppb) and 21 monitors for NO_2 (ppb). We computed the daily average $PM_{2.5}$ and NO_2 concentrations and the maximum average eight-hour O_3 concentration for each monitoring station. Using data from the three monitoring stations closest to the mother's geocoded residential address, we assigned air pollutant exposure estimates for each day of pregnancy from conception until delivery using inverse distance interpolation (Waller and Gotway, 2004).

2.4. Statistical analysis

All statistical analyses were conducted using SAS software (Version 9.4, SAS Institute, Cary, North Carolina). We used conditional logistic regression models to compute odds ratios (OR) and 95% confidence intervals (CI) to assess the association between apparent temperature and stillbirths in the warm season (n = 709). In crude models, we examined temperature exposures on each of lag days 1 to 6. We further examined moving exposures, i.e., means of lag days 1 to 2, 1 to 3, 1 to 4, 1 to 5 and 1 to 6. We also ran models adjusting for $PM_{2.5}$, NO_2 and O_3. We ran the same models to examine associations among mothers with (n = 87) and without (709) placental abruption. Finally, we examined potential effect measure modification by race/ethnicity among all-cause stillbirths by stratifying the full-adjusted models for the moving exposure average of lag days 1 to 6 by maternal race/ethnicity (Hispanic, non-Hispanic White and non-Hispanic Black).

We conducted three types of sensitivity analyses among all-cause stillbirths. We first examined whether removing lag day 1 exposures from moving exposure averages over subsequent lag days would affect the risk estimates, to account for the 48 h average time between intrauterine death and delivery (Gardosi et al., 1998). In other words, we examined moving exposures averages of lag days 2 to 3, 2 to 4, 2 to 5 and 2 to 6. Second, given that the bidirectional sampling approach identified control periods up to three weeks before or after the case period (8.5%), we conducted sensitivity analyses among all-cause stillbirths excluding cases with at least one control period outside of the warm season. Finally, we restricted the analysis to cases delivered during the hottest months, from June to August.

3. Results

Selected maternal characteristics are presented in Table 1. The mean (SD) age for all women with stillborn deliveries was 28 years (6.7). The majority of women had less than a high school education and approximately half were of Hispanic origin. The distribution of mean daily apparent temperature and daily air pollutant exposures over lag days 1 through 6 for case and control periods of stillbirths are presented in Table 2. Apparent temperature was weakly negatively correlated with NO_2 ($r = -0.37$) and O_3 ($r = -0.29$) and weakly correlated with $PM_{2.5}$ ($r = 0.11$) concentrations (cumulative of lag days 1 to 6) among stillbirth case periods.

In crude analyses, a 10 °F increase in apparent temperature was associated with a 25% (OR = 1.25, 95% CI: 1.09, 1.42 on lag day 5) to 34% (OR = 1.34, 95% CI: 1.17, 1.54 on lag day 2) increased risk of stillbirth on lag days 1 through 6 (Table 3). Similar results were observed in adjusted models and in models where exposure was operationalized using moving averages (i.e., means of lag days 1 to 2, 1 to 3, 1 to 4, 1 to 5 and 1 to 6), with the strongest risk associated with a 10 °F increase in mean apparent temperature during lag days 1 to 6 (adjusted OR = 1.45, 95% CI 1.18, 1.77). Further, the risk was elevated for Hispanic (OR = 1.60, 95% CI: 1.19, 2.15) and non-Hispanic Black women (OR = 1.61, 95% CI: 1.12, 2.30), but not for non-Hispanic White women (OR = 0.90, 95% CI: 0.54, 1.50) for exposures experienced over lag days 1 to 6 (Table 4).

In sensitivity analyses excluding exposures on lag day 1, we observed similar estimates for the risk of stillbirth among warm season deliveries for mean of lag days 2 to 3 (adjusted OR = 1.34, 95% CI: 1.13, 1.59), mean of lag days 2 to 4 (adjusted OR = 1.33, 95% CI: 1.11, 1.59), mean of lag days 2 to 5 (adjusted OR = 1.37, 95% CI: 1.13, 1.65) and mean of lag days 2 to 6 (adjusted OR = 1.39, 95% CI: 1.15, 1.69). In analyses excluding cases with cold-season control periods, we observed stronger estimates (adjusted OR = 1.96, 95% CI: 1.43, 2.69) among all-cause stillbirths associated with 10 °F increase in apparent temperature mean over lag days 1 to 6. Finally, for the same exposure period, we observed relatively strong risk of stillbirth (adjusted OR = 2.57, 95% CI: 1.72, 2.84) when we restricted analyses to deliveries in June, July and August.

Among stillbirths in mothers with placental abruption, we observed a 16% to 95% increase in risk of stillbirth associated with a 10 °F increase in apparent temperature on each of lag days 1 through 6, with the highest being on lag day 1 (OR = 1.96, 95% CI: 1.28, 3.02), lag day 2 (OR = 1.55, 95% CI: 1.06) and lag day 4 (OR = 1.45, 95% CI: 1.01, 2.09) (Table 5). We also observed similar elevated risks with moving exposure averages. Despite some loss of precision, the risk estimates were not attenuated when adjusted for $PM_{2.5}$, NO_2 and O_3. We observed risks of stillbirth that were lower in magnitude among mothers without placental abruption (Table S1).

4. Discussion

In an area characterized by high temperatures and humidity during the summer and independent of ambient air pollution exposures (i.e., $PM_{2.5}$, NO_2 and O_3), we found increased risk for stillbirths associated with increased mean apparent temperature in the week preceding delivery during the warm season, with the highest risks (37% and 25%) associated with a 10 °F increase in temperature on lag days 1 and 3, respectively. In evaluating mean apparent temperature in the six days preceding delivery, the risk was higher for stillbirths that occurred during June through August, among stillbirths with placental abruption and for Hispanic and non-Hispanic Black women.

Our results (equivalent to a 6% increased risk per 1 °C over lag days 2 to 6) are similar to those reported by Ha et al. (2017) but stronger in magnitude than in a previous study by Basu et al. (2016). For example, they reported a 10.4% change in risk per 10 °F increase in mean apparent temperature over lag days 2 to 6 during the warm season whereas we found a 39% increased risk per 10 °F. While Basu et al. reported similar results among women of different racial/ethnic groups (except for Asian women), we found increased risks of still births associated with increases in temperature for Hispanics and non-Hispanic Blacks, but not for non-Hispanic White women. Further, our findings of higher risks among stillbirths with placental abruption are supported by recent evidence from He et al. (2018) on the association between elevated maximum weekly temperatures and the risk for placental abruption at term. Although we cannot rule out the role of chance, our findings point to the potentially important role of placental abruption in the association between temperature and stillbirths.

One major strength of this investigation was the use of a case-crossover design, which minimized confounding and provided ample sample size to examine associations among a relatively small proportion of stillbirths caused by placental abruption. Our study also was located in a region with hotter and more humid temperatures than in previous investigations examining the role of temperature on increased risks for stillbirths. Further, a symmetric bidirectional sampling approach for selecting control periods before and after each case period minimized bias from temporal trends in temperature levels (Maclure and Mittleman, 2000). The case-crossover design also allowed us to minimize potential exposure misclassification of air pollutants due to residential mobility during pregnancy, as it covered a short period of time (no more than three weeks) before and after the event. However, while it is possible that some women may have still moved during this narrow period, there might not be a significant difference in exposure assessment between address at delivery and address at conception, as suggested by Lupo et al. (2010) in a study of residential mobility of pregnant women in Texas.

This study did not include fetal deaths of gestational age < 20 weeks (or of fetal birth weight < 350 g (g)), which could also be associated with increasing temperature exposures (Chambers, 2006). Also, we did not have information on other placental causes of stillbirth reported on the fetal death certificate, which would have enabled us to better understand the link between temperature, placental pathology and stillbirth. Further, there is evidence that fetal death certificates might not accurately report the true cause of death (placental or otherwise) (Greb et al., 1987; Lydon-Rochelle et al., 2005; Duke et al., 2008; Heuser et al., 2010). However, because the assignment of a case or control status in this study was independent of exposure status, selection bias arising from use of fetal death records is unlikely to have occurred. Another limitation is that while our apparent temperature exposure metric incorporated ambient and dew point temperature (the latter of which is a function of relative humidity), we did not have information on indoor temperature and the use of air conditioning systems in the home, the frequency of which might be unique to the study area. We also lacked information on activity patterns, such as time spent outdoors, although any exposure misclassification this may have introduced would have likely been non-differential and thus, would have tended to bias estimates toward the null.

5. Conclusion

To our knowledge, this is the first study in the published literature to examine the impact of temperature on stillbirth in a location characterized by hot and humid summers, as well as to examine the temperature-stillbirth association in mothers with and without placental abruption. We observed elevated risks for all stillbirths associated with temperature increases during the week prior to delivery, for Hispanic and non-Hispanic Black women, and for stillbirths in mothers with placental abruption.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

This work was supported in part by a National Institute for Occupational Safety and Health (NIOSH) Education and Research Center Grant (#5T42OH008421).

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Table 1

Selected sociodemographic characteristics of women with all-cause stillbirth and stillbirths caused by placental abruptions during the warm season (May-Sep), Harris County, Texas, 2008—2013.

Characteristic	All-cause stillbirths	Stillbirths caused by placental abruption
	n (%)[a]	n (%)[a]
Total	709 (100)	87 (100)
Maternal age (years)		
Mean ± SD	27.5 ± 6.7	27.1 ± 6.3
< 20	79 (11.1)	11 (12.6)
20–24	158 (22.3)	20 (23)
25–29	165 (23.3)	17 (19.5)
30–34	146 (20.6)	23 (26.4)
35–39	79 (11.1)	10 (11.5)
≥40	30 (4.2)	–
Missing	52 (7.3)	–
Maternal race		
Non-Hispanic White	109 (15.4)	18 (20.7)
Non-Hispanic Black	238 (33.6)	36 (41.4)
Hispanic	326 (46)	33 (37.9)
Other/unknown	36 (5.1)	
Maternal education		
High school or less	430 (60.7)	46 (52.9)
Some college	176 (24.8)	30 (34.5)
College or beyond	98 (13.8)	10 (11.5)
Missing	–	–
Prenatal care visits		
None	17 (2.4)	–
< 10	434 (61.2)	52 (59.8)
≥10	97 (13.7)	11 (12.6)
Missing	161 (22.7)	23 (26.4)
Smoking		
No smoking before or during pregnancy	677 (95.5)	82 (94.3)
Smoked 3 months before and during pregnancy	31 (4.4)	–
Missing	–	
Pre-pregnancy BMI (kg/m^2)[b]		
< 18.5	17 (2.4)	
18.5 to 24.9	220 (31)	31 (35.6)
25.0 to 29.9	172 (24.3)	18 (20.7)
30.0 to 34.9	95 (13.4)	11 (12.6)
≥35	100 (14.1)	12 (13.8)
Missing	105 (14.8)	15 (17.2)

Characteristic	**All-cause stillbirths**	**Stillbirths caused by placental abruption**
	n (%)[a]	**n (%)[a]**
Gestational Age (GA) (weeks)		
Mean ± SD	29 ± 6.6	30 ± 6.6

[a]Cases of 1 to 9 are not reported per Texas Department of State Health Services (DSHS) policy.

[b]Body mass index, weight (kg)/height (m^2).

Table 2

Estimated mean daily apparent temperature (°F) exposures on lag days 1 through 6 for case and control periods of stillbirths during the warm season (May-Sep), Harris County, Texas, 2008—2013.

Lag day	Case periods						Control periods					
	Mean ± SD	Min	Percentiles			Max	Mean ± SD	Min	Percentiles			Max
			25	50	75				25	50	75	
1	90.2 ± 7.1	51.1	87.3	91.6	95.2	99.7	89.2 ± 8.2	49.8	86.5	91.4	94.8	101.1
2	90.3 ± 6.8	51.1	87.1	91.9	95.4	101.1	89.1 ± 8.4	48.7	86.4	91.4	94.8	101.1
3	90.2 ± 6.7	59.9	87.3	91.6	95.2	101.1	89.2 ± 89.2	48.7	86.4	91.6	95	101.1
4	90.1 ± 6.6	59.5	87.1	91.4	95.2	99.7	89.2 ± 8.4	49.5	86.4	91.6	95	101.1
5	90.0 ± 6.8	55.8	86.9	91.2	94.8	101.1	89.2 ± 8.5	49.8	86.5	91.4	95.0	101.1
6	89.9 ± 7.2	51.1	87.1	91.4	94.8	101.1	89.0 ± 8.7	48.7	86.4	91.4	95.0	101.1

Table 3

Crude and adjusted[a] odds ratios (OR) and 95% confidence intervals (CI) for stillbirths associated with 10 °F increases in apparent temperature by lag day(s) during the warm season (May-Sep), Harris County, Texas, 2008—2013.

Lag day(s)	Crude	Adjusted
	OR (95% CI)	**OR (95% CI)**
1	1.30 (1.13, 1.49)	1.37 (1.16, 1.61)
2	1.34 (1.17, 1.54)	1.28 (1.08, 1.50)
3	1.31 (1.15, 1.50)	1.35 (1.15, 1.59)
4	1.28 (1.12, 1.47)	1.25 (1.07, 1.47)
5	1.25 (1.09, 1.42)	1.29 (1.10, 1.52)
6	1.26 (1.10, 1.44)	1.28 (1.09, 1.50)
1 to 2	1.36 (1.18, 1.57)	1.34 (1.14, 1.57)
1 to 3	1.39 (1.20, 1.61)	1.39 (1.16, 1.67)
1 to 4	1.41 (1.21, 1.64)	1.39 (1.16, 1.68)
1 to 5	1.43 (1.22, 1.67)	1.42 (1.17, 1.73)
1 to 6	1.45 (1.24, 1.70)	1.45 (1.18, 1.77)

[a]Adjusted for $PM_{2.5}$ (μg/m^3), NO_2 (ppb) and O_3 (ppb).

Table 4

Adjusted[a] odds ratios (OR) and 95% confidence intervals (CI) for stillbirths associated with 10 °F increases in apparent temperature over lag days 1 to 6 during the warm season (May-Sep), stratified by maternal race/ ethnicity, Harris County, Texas, 2008—2013.

Lag days	Non-Hispanic White	Non-Hispanic Black	Hispanic women
	OR (95% CI)	OR (95% CI)	OR (95% CI)
1 to 6	0.90 (0.54, 1.50)	1.61 (1.12, 2.30)	1.60 (1.19,2.15)

[a]Adjusted for $PM_{2.5}$ (μg/m^3), NO_2 (ppb) andO_3 (ppb).

Table 5

Crude and adjusted[a] odds ratios (OR) and 95% confidence intervals (CI) for stillbirths caused by placental abruptions associated with 10 °F increases in apparent temperature by lag day(s) in the warm season (May-Sep), Harris County, Texas, 2008—2013.

Lag day(s)	Crude	Adjusted
	OR (95% CI)	OR (95% CI)
1	1.96 (1.28, 3.02)	1.93 (1.15, 3.23)
2	1.55 (1.06, 2.27)	1.4 (0.87, 2.23)
3	1.37 (0.96, 1.94)	1.45 (0.93, 2.25)
4	1.45 (1.01, 2.09)	1.61 (1.02, 2.54)
5	1.3 (0.92, 1.84)	1.06 (0.98, 1.10)
6	1.16 (0.83, 1.62)	1.08 (0.72, 1.61)
1 to 2	1.49 (1.02, 2.18)	1.26 (0.81, 1.97)
1 to 3	1.7 (1.12, 2.57)	1.6 (0.95, 2.68)
1 to 4	1.71 (1.12, 2.61)	1.65 (0.97, 2.81)
1 to 5	1.68 (1.1, 2.56)	1.65 (0.96, 2.82)
1 to 6	1.62 (1.06, 2.47)	1.54 (0.89, 2.66)

[a]Adjusted for $PM_{2.5}$ (μg/m^3), NO_2 (ppb) andO_3 (ppb).